Remarks

Claims 76-102 were pending in the subject application. By this Amendment, claims 76, 90, 95, 96, and 101 been amended, and claim 91 has been canceled. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 76-90 and 92-102 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Supplemental Information Disclosure Statement (SIDS) under 37 C.F.R. §§ 1.97 and 1.98 for the Examiner's consideration.

Claims 90-102 have been rejected as obvious over claims 12-21 of U.S. Patent No. 6,127,172 under the judicially created doctrine of "obviousness-type" double patenting. Attached with this Amendment is a Terminal Disclaimer with respect to U.S. Patent No. 6,127,172, which obviates this rejection. Submission of the Terminal Disclaimer should not necessarily be construed as acquiescence to the "obviousness-type" double patenting rejection.

Claims 76-102 have been rejected under 35 U.S.C. §112, first paragraph, as nonenabled by the subject specification. The applicants respectfully submit that the subject specification enables the claims as filed. However, by this Amendment, the applicants have amended claim 76 to specify that the promoter is a heterologous early pox promoter or a non-pox promoter. Furthermore, the applicants have amended claims 90 and 101 to specify that the promoter is a non-pox promoter. Support for these amendments can be found, for example, at page 75, lines 11-24, and page 81, lines 15-24, of the subject specification, which indicates that promoters recognized by the cellular (not poxvirus) RNA polymerase of the host cell can be used.

The applicants have addressed each of the points raised in the Office Action in turn, in the paragraphs that follow. At page 5 of the Office Action, it stated that the specification does not provide an enabling disclosure for the use of any and all promoter sequences, other than a promoter sequence with early gene transcription activity. This statement appears to be predicated upon certain excerpts taken from the subject specification. For example, the Office Action points out that the subject specification, at pages 13-14, bridging paragraph, indicates that entomopox virus cannot productively infect mammalian cells and that gene expression is limited to early promoter activity.

Further, the Office Action notes that the subject specification indicates that late poxvirus promoters, such as AmEPV spheroidin or cowpox virus ATI, are inactive in mammalian cells infected with recombinant EPV. The Office Action then concludes that "the skilled artisan would not predict that any and all promoter sequences could express a heterologous gene of interest when encoded by a recombinant entomopox virus." As indicated in the preceding paragraph, the applicants have amended the claims to recite that the promoter sequence is a heterologous early pox promoter sequence or a non-pox virus promoter sequence.

The applicants will be submitting an Expert Declaration under 37 CFR § 1.132 by Dr. Richard Moyer at a later date. In his Expert Declaration, Dr. Moyer explains that the paragraph bridging pages 13-14 of the subject specification, which is cited in the outstanding Office Action, refers to the general observation that when using entomopox virus vectors containing entomopox promoters, genes under the control of early entomopox promoters will be expressed in a vertebrate cell, but genes under the control of late entomopox promoters will not. The applicants note that the paragraph bridging pages 13 and 14 of the subject specification cites two publications (Li *et al.* [1997] and Gauthier *et al.* [1995]), both of which describe experiments using entomopox virus vectors containing entomopox promoters. However, the distinction between "early" promoters and "late" promoters only finds context with respect to pox virus promoters (vertebrate and insect pox virus promoters). Dr. Moyer states in his Expert Declaration,

> ...when insect pox viruses infect vertebrate cells, early and only early pox virus promoters are active. This is likely because the early pox virus transcription apparatus is actually packaged within the virion particle as part of creating virions from the previous infection. In vertebrate cells, following early promoter-driven expression, the infection then crashes and eventually the input virus particles disintegrate after which the viral DNA is released into the vertebrate cell's cytoplasm; hence, the lack of late pox promoter-driven expression in vertebrate cells.

This observation is also made within the Li *et al.* publication (1997) at page 9557, second column, page 9560, second column, and page 9561, second column, which is cited in the Office Action. Furthermore, as indicated within the Li *et al.* publication at page 9561, second column, second paragraph, and at page 78, lines 3-7, of the subject specification, an exception to this phenomenon is when EPV vectors containing late pox promoters are supplied with certain factors *in trans* (*e.g.*, by co-infection with vaccinia virus), which at least partially rescue late gene expression.

Importantly, early pox virus promoters and (under certain circumstances) late pox promoters are not the only promoters that can be used in conjunction with an entomopox virus vector to achieve expression of a heterologous polynucleotide within a vertebrate cell. As disclosed at page 75, lines 11-24, and page 81, lines 15-24, of the subject specification, entomopox virus vectors containing genes under the control of non-pox virus promoters can also be utilized, as well. Non-pox promoters that are recognized by the vertebrate host cell's RNA polymerase, such as the cytomegalovirus (CMV) and herpes TK gene promoter, can be used to achieve stable transformation of the vertebrate host cell, expressing those heterologous genes that are under the control of the non-pox promoters. As disclosed at page 12, lines 21-27, of the subject specification, and as Dr. Moyer indicates in his Expert Declaration, preferred promoters are those constitutive or regulatable promoters capable of promoting sufficient levels of expression of the heterologous DNA contained in the viral vector in a vertebrate cell, such as the CMV and herpes TK gene promoters.

At pages 5 and 6 of the Office Action, it is stated that the subject specification does not provide an enabling disclosure for *in vivo* delivery of "therapeutically effective" recombinant viruses or vectors. Example 11, at page 79 of the subject specification, demonstrates the *in vivo* expression of β-galactosidase in mouse muscle using a TK-esp*lacZ* construct. The Office Action states that the working example only examines expression at day two, following injection, "and does not correlate the level or duration of gene expression with any therapeutic effect." The applicants submit that the claims of the subject application do not recite the requirement of a "therapeutic effect." Rather, the claims are directed to methods for delivering a polynucleotide encoding a protein to a vertebrate cell and expressing the polynucleotide in the vertebrate cell, recombinant entomopox virus vectors, viral particles, and vertebrate cells comprising such recombinant entomopox virus vectors.

Moreover, claims 76-89 are directed to the delivery of a recombinant entomopox virus vector to a cell; however, it is noted that the inventive concept pertains to the entomopox vector. This is to say, the novel vector is considered a 'tool' for delivery of a gene to a cell. As such, it is noted that the specification teaches delivery of a gene to a cell using the entomopox vector of the invention in both *in vitro* and *in vivo* respects. In addition, while the present inventors were the first to demonstrate gene delivery by use of the entomopox virus vector to mammalian cells, numerous other viral vectors find readily apparent uses in the state of the art (pre- and post-filing) as a tool for both

in vitro and *in vivo* uses. [US Patent Nos. 5,972,597; 6,312,383; 5,672,344; Kramm *et al.* (1996) *Hum. Gene Ther.* 7: 291-300; Sewell *et al.* (1997) *Arch. Otolaryngol. Head Neck Surg.* 123: 1298-1302; Cardoso *et al.* (1993) *Hum. Gene Ther.* 4: 411-418; and Podda *et al.* (1992) *PNAS* 89: 9676-9680; for example.] Furthermore, it is noted that effects of the expression of gene products of transduced cells *in vivo*, such as gene therapy, are not recited in the claim. The courts have set the following precedence, "[t]hat the claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims." *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir.1983), 469 U.S. 835 (1984).

Furthermore, Dr. Moyer indicates in his Expert Declaration that, while expression of the β-galactosidase gene was examined two days following infection with the recombinant entomopox virus vector, one of ordinary skill in the art would expect that expression of the foreign gene would be sustained beyond the two days at which the tissue was excised, particularly if other non-pox promoters recognized by the RNA polymerase of the vertebrate cells were used, such as non-pox, tissue-specific promoters.

At page 6, the Office Action indicates that the specification provides no guidance as to other routes or sites of injection, or dosage of virus or cells. The applicants submit that it is not necessary to specify the dosage or administration routes where such information can be obtained by one of ordinary skill in the art without undue experimentation, as is the case here. *In re Johnson*, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 144 USPQ 637, 643 (CCPA 1965).

At page 6, the Office Action cites Li *et al.* (1997) for reporting the small amount of expression observed in lymphoid cells infected with recombinant entomopox virus. The Office Action states that, therefore, the skilled artisan would not predict that the entomopox viruses of the instant invention could be used to express therapeutic levels of protein in lymphoid cells, which are associated with certain disorders, such as Burkitt's lymphoma. As acknowledged at page 9 of the Office Action, the Li *et al.* publication reports experiments using beta-galactosidase enzyme under the control of pox promoters (the cowpox virus A-type inclusion (ATI) promoter and the Melolontha EPV fusolin promoter). However, as indicated by Dr. Moyer in the Declaration, the ordinarily skilled artisan would expect that entomopox virus-mediated expression of a foreign gene can be achieved in lymphoid tissue using a non-pox promoter recognized by the RNA polymerase of the

vertebrate cell, particularly if a lymphoid tissue-specific promoter is utilized. Therefore, the applicants respectfully submit that the invention, as now claimed, is fully enabled by the subject specification. Accordingly, in view of the amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 90, 92, 95, 97, and 100-102 have been rejected under 35 U.S.C. §102(b) as anticipated by Li *et al.* (1997) *J. Virol.*, Vol. 71 (12), 9557-9562. The applicants submit that the Li *et al.* publication does not teach or suggest the applicants claimed invention. However, by this Amendment, claims 90 and 101 have been amended to specify that the polynucleotide encoding a protein is operably linked to a non-pox virus promoter sequence. The Office Action indicates that the Li *et al.* publication discloses an AmEPV vector encoding the beta-galactosidase enzyme under the control of the heterologous cowpox virus A-type inclusion (ATI) promoter or the heterologous Melolontha EPV fusulin promoter, a viral particle comprising the vector, and insect cells infected with the viral partical and expressing beta-galactosidase protein. Neither the cowpox virus ATI promoter nor the Melolontha EVP fusulin promoter are non-pox virus promoters. Therefore, the applicants respectfully submit that the Li *et al.* publication does not teach or suggest the invention, as now claimed.

Furthermore, the applicants submit that the claimed subject matter is entitled to the priority date of application serial no. 09/086,651, which is May 29, 1998. The Li *et al.* publication indicates that it was published in December, 1997, which is less than one year before the applicants' claimed priority date. Therefore, the rejection set forth under 35 U.S.C. §102(b) is not appropriate. The applicants also note that the Office Action Summary does not indicate that there has been an acknowledgement of a claim of domestic priority under 35 U.S.C. §119(e) and 35 U.S.C. §120. The applicants respectfully request acknowledgement of a claim of domestic priority.

The applicants also wish to point out that, to the extent that the Li *et al.* publication is relied upon as prior art, this reference is the work of the current applicants. Although an additional author is named on the publication, the additional author did not contribute to the conception of the claimed subject matter. It is well recognized that the laws which govern inventorship determinations differ from the etiquette and customs applied to authorship determination. "One's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory

bar." *In re Facius*, 161 USPQ 294, 301 (CCPA 1969). The Li *et al.* publication is a disclosure by the inventors of their own work which was published less than one year prior to the effective filing date of the subject application. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

The Office Action indicates that the declaration of record is defective because it is not executed. In response to a Notice to File Missing Parts, the applicants submitted three new Declaration and Power of Attorney documents executed, respectively, by Dr. Moyer, Li, and Bawden, with the transmittal letter filed November 22, 2000. Copies of the fully executed Declaration and Power of Attorney documents with the transmittal letter are submitted herewith for the Examiner's convenience. In addition, the applicants note that these executed documents identify the specification by attorney docket number (UF-221C1XC1), which was on the specification as filed. MPEP 601.01(a) indicates that an attorney docket number which was on the specification as filed will be accepted as complying with the identification requirement of 37 CFR § 1.163. Therefore, the applicants respectfully request reconsideration and withdrawal of this objection.

In view of the foregoing remarks and amendments to the claims, and the documents submitted herewith, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Glenn P. Ladwig

Glenn P. Ladwig
Patent Attorney
Registration No. 46,853
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
2421 NW 41st Street, Suite A-1
Gainesville, FL 32606-6669

Attachments: Petition and Fee for one-month Extension of Time
Marked-Up Version of Amended Claims
Supplemental Information Disclosure Statement, with Form PTO-1449
Terminal Disclaimer
Copies of executed Declaration and Power of Attorney forms submitted November 22, 2000, with transmittal letter

MARKED-UP VERSION OF AMENDED CLAIMS

Claim 76 (Amended):

A method for delivering a polynucleotide encoding a protein to a vertebrate cell, said method comprising introducing into said vertebrate cell a recombinant entomopox virus vector comprising said polynucleotide operably linked with a [promoter sequence] heterologous early pox promoter sequence or a non-pox virus promoter sequence, thereby delivering and expressing said polynucleotide encoding said protein in said vertebrate cell.

Claim 90 (Amended):

A recombinant entomopox virus vector comprising a polynucleotide encoding a protein operably linked with a [heterologous] non-pox virus promoter sequence.

Claim 95 (Amended):

The vector according to claim 90, wherein said [heterologous] non-pox virus promoter sequence is capable of driving expression of said polynucleotide encoding said protein.

Claim 96 (Amended):

The vector according to claim 95, wherein said [heterologous] non-pox virus promoter sequence is selected from the group consisting of CMV and herpes TK.

Claim 101 (Amended):

A cell comprising a recombinant [entomoxpox] entomopox virus vector comprising a polynucleotide encoding a protein operably linked with a [heteroJogous] non-pox virus promoter sequence.